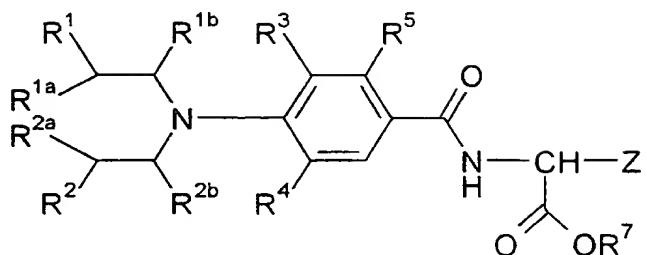


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CLAIMS

1. A compound of Formula I:



wherein:

- 5 R¹ is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;
 R² is -Cl, -Br, -I, -OSO₂CH₃, or -OSO₂Ph ;
 wherein Ph denotes a phenyl group which is
 optionally substituted with 1, 2, 3, 4 or 5 substituents
 independently selected from a C₁₋₄ alkyl group, -F, -Cl,
 10 -Br, -I, -CN, or -NO₂;
- 15 R^{1a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
 R^{2a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
 R^{1b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
 R^{2b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ;
- 20 R³ is -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CH₃, -CF₃,
 -SF₅, -SCF₃, or -CF₂CF₃ ;
- 25 R⁴ is -H, -F, -Cl, -Br, -I, -OCHF₂, -C≡CH, -OCF₃, -CH₃,
 -CF₃, -SF₅, -SCF₃, or -CF₂CF₃ ;
- 30 R⁵ is -H or -F;
 with the proviso that if R⁴ is -H, then R³ is not -F;
- 35 R⁷ is -H, -C(CH₃)₃, or -CH₂-CH=CH₂ ;

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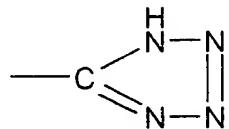
Z is -CH₂-T-W ;

T is -CH₂- , -O- , -S- , -(S=O)- , or -(SO₂)- ;

the group -CH₂-T- may optionally be substituted with 1 or 2 substituents, denoted Q¹ and Q² respectively, on carbon, wherein Q¹ and Q² are independently a C₁₋₄alkyl group or a halogen; or, when Q¹ and Q² are bonded to adjacent carbon atoms, Q¹ and Q² together may form a C₃₋₄alkylene radical optionally substituted with 1, 2, 3 or 4 substituents independently selected from C₁₋₄alkyl groups and halogens;

W is one of:

- (1) -COOH ;
- (2) -(C=O)OR⁸ ;
- (3) -(C=O)NR⁹R⁹ ;
- (4) -SO₂NHR¹⁰ ;
- (5) -SO₂OR¹¹ ;
- (6) -PO₃R¹¹R¹¹ ;
- (7) a tetrazol-5-yl group:



- (8) -CONH-SO₂R¹² ; and,
- (9) -M-Het;

with the proviso that if T is -O- , -S- , -(S=O)- , or -(SO₂)- , then W is not -COOH;

wherein:

R⁸ is a C₁₋₆alkyl group, a C₃₋₆cycloalkyl group, a C₅₋₂₀aryl group, or -CH₂-CH=CH₂ ;

wherein the C₅₋₂₀aryl group may optionally be substituted on carbon with from 1 to 4 substituents

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selected from -COOH, -OH, -NH₂, -CH₂NH₂, -(CH₂)₁₋₄COOH, tetrazol-5-yl, and -SO₃H;

R⁹ is independently -H, a C₁₋₆alkyl group, a C₃₋₆cycloalkyl group, a C₅₋₂₀aryl group, a C₇₋₉aralkyl group, or a 5 C₅₋₂₀heteroaryl group linked to N via carbon;

wherein the C₅₋₂₀aryl group, the C₅₋₂₀heteroaryl group, and aryl moiety of the C₇₋₉aralkyl group may optionally be substituted on carbon with from 1 to 4 substituents selected from -COOH, -OH, -NH₂, -CH₂NH₂, -(CH₂)₁₋₄COOH, tetrazol-5-yl, and -SO₃H;

10 and wherein the C₃₋₆cycloalkyl group may optionally carry a methyl group;

R¹⁰ is a C₁₋₆alkyl group, -CH₂-CH=CH₂, a C₃₋₆cycloalkyl group, a C₁₋₄haloalkyl group (e.g., -CF₃, -CH₂CF₃), or a 15 C₅₋₂₀aryl group;

wherein the C₅₋₂₀aryl group, the C₅₋₂₀heteroaryl group, and aryl moiety of the C₇₋₉aralkyl group may optionally be substituted on carbon with from 1 to 4 substituents selected from -COOH, -OH, -NH₂, -CH₂NH₂, -(CH₂)₁₋₄COOH, tetrazol-5-yl, and -SO₃H;

20 and wherein the C₃₋₆cycloalkyl group may optionally carry a methyl group;

R¹¹ represents -H, a C₁₋₆alkyl group, or a C₃₋₆cycloalkyl group;

25 R¹² is one of:

- (a) a C₃₋₇cycloalkyl group;
- (b) a C₁₋₆alkyl group, optionally substituted with one or more of: a phenyl group; a phenyl group with from 1 to 5 substituents selected from halogen, -NO₂, -CF₃, C₁₋₄alkyl, C₁₋₄alkoxy, -NH₂, -NHCOPH₃, -CONH₂, -OCH₂COOH, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂,

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-NHCOOC₁₋₄alkyl, -OH, -COOH, -CN and -COOC₁₋₄alkyl; a C₁₋₄alkyl group; a C₁₋₄haloalkyl group; or a halogen; and,

(c) a C₁₋₆perfluoroalkyl group;

5 M represents -S-, -SO-, or -SO₂- ; and,

Het represents a 5 or 6 membered heterocyclic aromatic ring linked to M via a carbon atom of the aromatic ring, said aromatic ring containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of O, N and S said aromatic ring optionally being substituted on carbon atoms of the ring with 1, 2, 3 or 4 substituents selected from the group consisting of -OH, -SH, -CN, -CF₃, NH₂ and halogen.

2. A compound according to claim 1, wherein:

15 R¹ and R² are independently -I, -Br, or -Cl.

3. A compound according to claim 1, wherein:

R¹ and R² are both -I.

4. A compound according to any one of claims 1 to 3, wherein:

20 R^{1a}, R^{1b}, R^{2a}, R^{2b} are each independently -H or -CH₃.

5. A compound according to any one of claims 1 to 3, wherein:

R^{1a}, R^{1b}, R^{2a}, R^{2b} are all -H.

6. A compound according to any one of claims 1 to 5, wherein:

25 R³ and R⁴ are -CF₃ and -H, respectively.

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7. A compound according to any one of claims 1 to 5,
wherein:

R³ and R⁴ are both -F.

8. A compound according to any one of claims 1 to 5,
5 wherein:

R³ and R⁴ are -CF₃ and -H, respectively; and,
R⁵ is -H.

9. A compound according to any one of claims 1 to 5,
wherein:

10 R³ and R⁴ are both -F; and,
R⁵ is -F.

10. A compound according to any one of claims 1 to 5,
wherein:

R³ and R⁴ are both -F; and,
15 R⁵ is -H.

11. A compound according to any one of claims 1 to 10,
wherein:

Z is -CH₂-T-C(=O)OH or -CH₂-T-C(=O)OR⁸; and,
T is -CH₂-.

- 20 12. A compound according to any one of claims 1 to 11,
wherein:

R⁸ is -H, -C(CH₃)₃, or -CH₂-CH=CH₂.

13. A compound selected from:

25 {3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoyl}-L-
glutamic acid; and,
the di-tert-butyl ester thereof.

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14. A compound selected from:

3,5-difluoro-4-[bis(2-chloroethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

5 15. A compound selected from:

{3,5-difluoro-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

16. A compound selected from:

10 {2,3,5-trifluoro-4-[bis(2-chloroethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

17. A compound selected from:

15 {2,3,5-trifluoro-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

18. A compound selected from:

20 {2,3,5-trifluoro-4-[bis(2-iodoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

19. A compound selected from:

{3,5-difluoro-4-[bis(2-bromopropyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

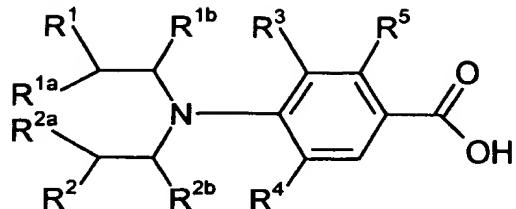
25 20. A compound selected from:

{3-trifluoromethyl-4-[bis(2-bromoethyl)amino]benzoyl}-L-glutamic acid; and,
the di-tert-butyl ester thereof.

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21. A compound of Formula II:



wherein:

 R^1 is $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OSO}_2\text{CH}_3$, or $-\text{OSO}_2\text{Ph}$; R^2 is $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OSO}_2\text{CH}_3$, or $-\text{OSO}_2\text{Ph}$;

wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C_{1-4} alkyl group, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CN}$, or $-\text{NO}_2$;

 $\text{R}^{1\text{a}}$ is $-\text{H}$, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group ; $\text{R}^{2\text{a}}$ is $-\text{H}$, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group ; $\text{R}^{1\text{b}}$ is $-\text{H}$, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group ; $\text{R}^{2\text{b}}$ is $-\text{H}$, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group ; R^3 is $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OCF}_2$, $-\text{C}\equiv\text{CH}$, $-\text{OCF}_3$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{SF}_5$, $-\text{SCF}_3$, or $-\text{CF}_2\text{CF}_3$; R^4 is $-\text{H}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OCF}_2$, $-\text{C}\equiv\text{CH}$, $-\text{OCF}_3$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{SF}_5$, $-\text{SCF}_3$, or $-\text{CF}_2\text{CF}_3$; R^5 is $-\text{H}$ or $-\text{F}$;

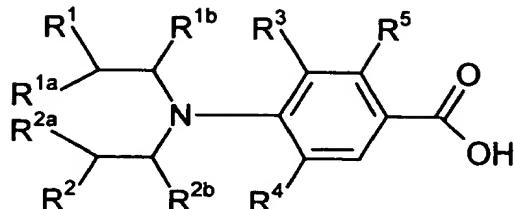
with the proviso that if R^4 is $-\text{H}$, then R^3 is not $-\text{F}$;
and,

with the proviso that if R^1 is $-\text{Cl}$, R^2 is $-\text{Cl}$, $\text{R}^{1\text{a}}$ is $-\text{H}$, $\text{R}^{2\text{a}}$ is $-\text{H}$, $\text{R}^{1\text{b}}$ is $-\text{H}$, $\text{R}^{2\text{b}}$ is $-\text{H}$, R^4 is $-\text{H}$, and R^5 is $-\text{H}$, then R^3 is not $-\text{CH}_3$.

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22. A compound of Formula II:



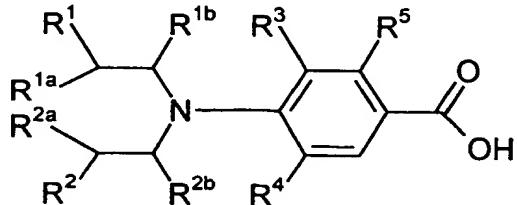
wherein:

 R^1 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$; R^2 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C_{1-4} alkyl group, -F, -Cl, -Br, -I, -CN, or $-NO_2$;

 R^{1a} is -H, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group; R^{2a} is -H, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group; R^{1b} is -H, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group; R^{2b} is -H, a C_{1-4} alkyl group, or a C_{1-4} haloalkyl group; R^3 is -F, -Cl, -Br, -I, $-OCHF_2$, $-C\equiv CH$, $-OCF_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$; R^4 is -H, -F, -Cl, -Br, -I, $-OCHF_2$, $-C\equiv CH$, $-OCF_3$, $-CF_3$, $-SF_5$, $-SCF_3$, or $-CF_2CF_3$; R^5 is -H or -F;with the proviso that if R^4 is -H, then R^3 is not -F.

23. A compound of Formula II:



wherein:

 R^1 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$; R^2 is -Cl, -Br, -I, $-OSO_2CH_3$, or $-OSO_2Ph$;

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wherein Ph denotes a phenyl group which is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from a C₁₋₄ alkyl group, -F, -Cl, -Br, -I, -CN, or -NO₂; R^{1a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ; R^{2a} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ; R^{1b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ; R^{2b} is -H, a C₁₋₄alkyl group, or a C₁₋₄haloalkyl group ; R³ and R⁴ are -CF₃ and -H, respectively, or R³ and R⁴ are both -F; R⁵ is -H or -F.

24. A compound according to any one of claims 21 to 23, wherein:
R¹ and R² are independently -I, -Br, or -Cl.
25. A compound according to any one of claims 21 to 23, wherein:
R¹ and R² are both -I.
26. A compound according to any one of claims 21 to 25, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are each independently -H or -CH₃.
27. A compound according to any one of claims 21 to 25, wherein:
R^{1a}, R^{1b}, R^{2a}, R^{2b} are all -H.
28. A compound according to any one of claims 21 to 27, wherein:
R³ and R⁴ are -CF₃ and -H, respectively.
29. A compound according to any one of claims 21 to 27, wherein:
R³ and R⁴ are both -F.

Amend
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30. A compound according to any one of claims 21 to 27, wherein:
 R^3 and R^4 are $-CF_3$ and $-H$, respectively; and,
 R^5 is $-H$.
31. A compound according to any one of claims 21 to 27, wherein:
 R^3 and R^4 are both $-F$; and,
 R^5 is $-F$.
32. A compound according to any one of claims 21 to 27, wherein:
 R^3 and R^4 are both $-F$; and,
 R^5 is $-H$.
33. 3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoic acid.
34. 3,5-difluoro-4-[bis(2-chloroethyl)amino]benzoic acid.
35. 3,5-difluoro-4-[bis(2-bromoethyl)amino]benzoic acid.
36. 2,3,5-trifluoro-4-[bis(2-chloroethyl)amino]benzoic acid.
37. 2,3,5-trifluoro-4-[bis(2-bromoethyl)amino]benzoic acid.
38. 2,3,5-trifluoro-4-[bis(2-iodoethyl)amino]benzoic acid.
39. 3,5-difluoro-4-[bis(2-bromopropyl)amino]benzoic acid.
40. 3-trifluoromethyl-4-[bis(2-bromoethyl)amino]benzoic acid.

ART 34 AMENDMENT

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41. A two-component system comprising:

- (i) a first component capable of delivering a carboxypeptidase enzyme to the interior or exterior of a target cell or a vector encoding said enzyme to the interior of said cell such that said vector expresses said enzyme in said cell, and
- (ii) a prodrug of according to any one of claims 1 to 20 capable of being converted by said enzyme into a drug according to any one of claims 21 to 40.

42. A kit comprising:

- (a) a compound according to any one of claims 1 to 20; and,
- (b) one of:
 - (i) an immunoglobulin/enzyme fusion protein or conjugate in which the immunoglobulin is specific for a cellular antigen and the enzyme is a carboxypeptidase enzyme;
 - (ii) a ligand/enzyme conjugate or fusion protein, the ligand being specific for a cellular antigen and the enzyme is a carboxypeptidase enzyme;
 - (iii) a vector which encodes a carboxypeptidase enzyme which can be expressed in a cell.

43. A composition comprising a compound according to any one of claims 1 to 40, and a pharmaceutically acceptable carrier or diluent.

44. A compound according to any one of claims 1 to 40 for use in a method of treatment of the human or animal body.

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45. A compound according to any one of claims 1 to 40 for use in a method of treatment of cancer of the human or animal body.
46. Use of a compound according to any one of claims 1 to 40 for the manufacture of a medicament for use in the treatment of cancer.
47. A method for the treatment of cancer comprising administering to a subject suffering from cancer a therapeutically-effective amount of a compound according to any one of claims 1 to 40.